DETAILED ACTION

A request for continued examination (RCE) under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 4/11/11 has been entered. Applicant's amendment and response received with the RCE submission on 4/11/11 have also been entered. Claims 1-116 are now canceled and new claims 117-141 have been added. Of these, claims 131-140 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on 2/1/10. Claims 117-130 and 141 are currently under examination. An action on the merits follows.

Those sections of Title 35, US code, not included in this action can be found in a previous office action.

Claim Rejections - 35 USC § 112

The rejection of previously pending claims 55-57, 59-68, and 110-116 under 35 U.S.C. 112, first paragraph, for scope of enablement is withdrawn over the canceled claims and maintained over new claims 117-130 and 141. Applicant's amendments and arguments have been fully considered but have not been found persuasive in overcoming the rejection for reasons of record as discussed in detail below.

The rejection of record identified the following scope of enablement: 1) a transgenic mouse in which both endogenous genomic copies of the SERCA2 gene contain two loxP sites flanking exons 2 and 3, and whose genome further comprises a MerCreMer transgene under transcriptional control of the α-MHC promoter, and 2) a transgenic mouse model of heart failure wherein said transgenic mouse model is made by administering tamoxifen to a transgenic mouse in which both endogenous genomic copies of the SERCA2 gene contain two loxP sites flanking exons 2 and 3, and whose genome further comprises a MerCreMer transgene under transcriptional control of the α-MHC promoter, wherein the administration of tamoxifen result in the Cre mediated deletion of exons 2 and 3 in both copies of the SERCA2 gene, and wherein the mouse develops heart failure by day 52 following tamoxifen administration.

The applicant states that new independent claim 117 recites a transgenic mouse whose genome comprises a homozygous disruption in an endogenous Serca2 gene in heart cells following expression of a site-specific recombinase of heterologous origin, where the disruption of the endogenous Serca2 gene results in a lack of expression of a functional Serca2 protein in heart cells. The applicant argues that the claims are now limited to a homozygous disruption in the Serca2 gene and further that dependent claim 118 recites a phenotype of defective Ca2+ handling, reduced Ca2+ pumping ability, decreased heart contractility and heart failure. Thus the applicant concludes that new claims 117-130 and 141 are enabled.

In response, it is first noted that previous claim sets were drawn to two different types of mouse, one which included loxP sites in a Serca gene, and one with a null mutation in a Serca gene. In other words, the previous claim sets included claims to the mouse before homologous recombination of the loxP sites resulted in a disruption of a Serca gene, and a mouse in which

homologous recombination has already occurred resulting in disruption of a Serca gene. The instant claims contain two independent claims. Claim 117, as noted by the applicant, is drawn to a mouse in which homologous recombination has already occurred and which has a homozygous disruption in an endogenous Serca2 gene following expression of a site-specific recombinase of heterologous origin. New claim 141 is broader and simply recites that the mouse has a homozygous disruption of an endogenous Serca2 gene in heart cells. Thus, none of the instant claims read on a mouse before disruption of the Serca2 gene has occurred. Further, none of the instant claim, with the exception of claim 130, recite the inclusion of a loxP site(s) in the Serca2 gene, and further either do not recite the presence or activity of a site-specific recombinase (claim 141), or read broadly on the use of any site-specific recombinase. It is also noted that none of the claims place any limitation on when the Serca2 gene has been disrupted in the mouse, i.e. pre-natal, post-natal, etc. In addition, the claims, with the exception of claim 130, encompass any type of disruption to the endogenous Serca2 gene which results in the lack of expression of a functional Serca2 protein in heart cells.

Previous office actions have stated that it is well established in case law that the specification must teach those of skill in the art how to make and how to use the invention as broadly claimed. *In re Goodman*, 29 USPQ2d at 2013 (Fed. Cir. 1994), citing *In re Vaeck*, 20 USPQ2d at 1445 (Fed. Cir. 1991) (emphasis added by examiner). 35 U.S.C. § 112 also requires that the scope of the claims must bear a reasonable correlation to the scope of enablement provided by the specification to persons of ordinary skill in the art. *In re Fisher*, 166 USPQ 18, 24 (CCPA 1970). With this in mind, the previous office actions analyzed the specification in direct accordance to the factors outlined in *In re Wands*, namely 1) the nature of the invention, 2)

the state of the prior art, 3) the predictability of the art, 4) the amount of direction or guidance present, 5) the presence or absence of working examples, 6) the quantity of experimentation necessary, 7) the relative skill of the skilled artisan, and 8) the breadth of the claims, and presented detailed scientific reasons for the finding of a lack of enablement for full scope of the invention as claimed. It is also noted that case law including the Marzocchi decision sanctions both the use of sound scientific reasoning and printed publications to support a holding of non-enablement (see *In re Marzocchi* 169 USPQ 367, and *Ex parte Sudilovsky* 21 USPQ2d 1702).

The previous office action pointed out that the specification fails to provide an enabling disclosure for making the breadth of transgenic mice encompassed by the claims, or for using the breadth of transgenic mice encompassed by the claims to produce a mouse model of heart disease. In regards to making the breadth of mice encompassed by the claims, it was acknowledged that the specification provides sufficient disclosure for making a transgenic mouse in which two or more loxP site have been inserted into a Serca2 ATPase gene; however, it was also noted that the specification fails to provide an enabling disclosure for making a transgenic mouse which further comprise a recombinase gene, such as Cre recombinase, that is expressed and active during embryonic and neonatal development. The prior art clearly teaches that the lack of Serca2 during embryogenesis in mice results in an embryonic lethal phenotype such that no Serca2 -/- mice are produced (see Periasamy et al., of record). Thus, the prior art clearly establishes that transgenic mice useful as a model of disease cannot be made where the genome of the mouse comprises two loxP or any other recombination sites in a Serca ATPase gene and which further comprises a heterologous nucleic acid encoding a Cre recombinase or any other recombinase where an active form of the recombinase is expressed during embryonic

development. These embodiments are encompassed by the instant claims. Further, since neither the prior art nor the instant specification definitively teaches the reasons for early lethality in Serca2 negative mice, i.e. which organ(s)or tissue(s) affected by the lack of a Serca ATPase gene are the cause of death, the skilled artisan would not have been able to predict without undue experimentation whether tissue specific expression of the recombinase in any particular tissue, including heart, could avoid the lethal phenotype associated with a homozygous Serca2 deletion during embryonic development.

The previous office action further discussed that the specification does not provide an enabling disclosure for making or using a transgenic mouse which comprises two or more recombination sites in any location of a Serca ATPase gene and which further comprises any inducible Cre recombinase or other recombinase gene. With the exception of claim 130, the claims as written no longer refer to the presence of loxP sites in the Serca2 gene, and therefore place no limitation on the placement of recombination sites in the Serca2. While the working examples provide specific guidance for the insertion of loxP sites flanking exons 2 and 3 of the Serca2 gene such that recombination of the sites creates a null mutation, the claims are not so limited and encompass the generation of any deletion in the genomic gene sequence. The specification provides no guidance for the enormous number of potential mutations to the genomic gene, or the consequences of any of these mutations on expression of a protein or partial protein product from the mutated gene. The specification further fails to provide any guidance as to the activity or lack thereof of any partial Serca ATPase gene product. Thus, with the exception of the deletion of exons 2 and 3 of the Serca2 gene, the specification fails to provide the requisite guidance for the phenotype of the genus of transgenic mice produced by

recombination of the inserted recombination sites as claimed. Note that "case law requires that the disclosure of an application shall inform those skilled in the art how to use applicant's alleged discovery, not to find out how to use it for themselves." *In re Gardner* 166 USPQ 138 (CCPA) 1970.

In regards to the generation of a null deletion in a Serca2 gene, the specification teaches that the embryonic lethal phenotype of a Serca2 negative mouse can be avoided by using an inducible recombinase system such that the timing of deletion of the Serca2 gene can be controlled and delayed until after birth. However, the working examples clearly demonstrate the complexity and unpredictability in choosing an inducible system which is capable of producing a homozygous deletion through recombination of inserted recombination sites. The working example reports a first attempt to generate an inducible Cre and homozygous floxed Serca2 mouse where the inducible Cre system comprises MLC-2v Cre. The working example teaches that Serca2-flox mice, whose genome comprises a homozygous insertion of loxP sites flanking exons 2 and 3 of the Serca2 gene, were crossed with MLC-2v Cre knock-in mice. However, the specification reports that the inventors were in fact unable to generate the expected Serca2 flox/flox MLC2v wt/Cre mouse. Further analysis revealed that linkage between the atap2a2 and myl2 genes on chromosome 5 was 100%, thus preventing generation of the Serca2 flox/flox MLC2v wt/Cre genotype. However, when the applicant's switched to a different inducible Cre system, where the encoded Cre protein was an inactive Mer-Cre-Mer protein whose activity can be induced by tamoxifen, the applicants were able to generate Serca2 flox/flox MCM mice. The working example using this mouse further demonstrates knock out of Serca2 following tamoxifen administration to adult mice resulting in the development of heart failure by day 52.

However, for the reasons discussed above and below, this single example of specific mouse genotype which generates a heart failure phenotype useful as a disease model, does not provide enablement for the scope of the instant claims as written, including claim 130, which continues to encompass a mouse in which recombination has been induced at any developmental stage.

Therefore, it is maintained that in view of the art recognized unpredictability in determining the phenotype of transgenic or knockout mouse even when the activity of the gene has been extensively studied *in vitro*, and the unpredictability of generating a mouse model for human disease based on the activity of the gene in humans, the unpredictability in correlating any observed phenotype in a knockout mouse with gene disruption as acknowledged by the prior art, the art recognized problems with early lethality in Serca2 knockout mice, the unpredictability in using any inducible recombinase system to generate a homozygous floxed Serca ATPase/ Cre mouse as evidenced by the working examples, the breadth of potential disruptions to the Serca2 gene encompassed the claims, and the general breadth of the claims as written, it would have required undue experimentation to make and use the scope of the instant invention as claimed.

The rejection of claim 56 under 35 U.S.C. 112, second paragraph, for indefiniteness is withdrawn in view of the cancellation of this claim.

Claim 130 is newly rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 130 depends on claim 117. Claim 117 recites a transgenic mouse whose genome comprises a homozygous disruption in an endogenous Serca2 gene in heart cells

following expression of a site-specific recombinase of heterogenous origin. Claim 130, however, recites that the both of the endogenous Serca2 genes are modified by two loxP sites positioned within introns of the Serca2 gene flanking exons 2 and 3. The limitations of claim 130 conflict with the limitations of claim 117, since in claim 117 the recombinase has been expressed and recombination of the loxP sites removes exons 2 and 3 and one of the loxP sites, thus creating the disruption in the Serca2 gene. Therefore, the claims are confusing and the metes and bounds of the claims cannot be determined.

Claim Rejections - 35 USC § 103

The rejection of previously pending claims 55-57, 59-68, and 110-116 under 35 U.S.C. 103(a) as being unpatentable over Periasamy et al. (1999) J. Biol. Chem., Vol. 274(4), 2556-2562, in view of Sohal et al. (2001) Circ. Res., Vol. 89, 20-25 is withdrawn over the canceled claims and maintained over new claims 117-130 and 141. Applicant's amendment, arguments, and the Declaration under 37 CFR 1.132 by Dr. Wuytack, who is not an inventor of the instant invention, have been fully considered but have not been found persuasive in overcoming the rejection for reasons of record as discussed in detail below.

The applicant argues that Periasamy teaches away from making the instant mouse as claimed because Periasamy teaches that the homozygous Serca2 mutants were embryonic lethal such that they were forced to use heterozygous mice in their experiments. The applicant further argues that the skilled artisan would have expected that loss of Serca2, even in an adult, to be lethal because Serca2 is critical for life at all stages. The applicant also reiterates their argument

concerning unexpected results, further pointing to the Declaration under 37 CFR 1.132 by Dr. Wuytack, submitted with the instant response, which states that in the opinion of Dr. Wuytack et al., "..it would be highly probably that a mouse lacking a functional Serca2 ATPase at the adult stage would not survive for long, and in particular, not survive for more than about one week" (Declaration of 4/11/11, page 2). The declaration further states that the observed survival of the mice disclosed in the instant specification for up to 7 or 8 weeks is much longer than predicted.

In response, it is first noted that none of pending claims place any limitation on the length of survival of the transgenic mouse. A mouse that survives for even one day following knockout of both copies of the Serca2 gene would meet the limitations of the instant claims. It is further noted that the Declaration by Dr. Wuytack et al. does not state that homozygous knockout of Serca2 in an adult would be instantly lethal. As set forth above, Dr. Wuytack et al. states that in his opinion based on the state of the art as of 2003, that it would be probable that the mice as claimed would not survive for more than about one week. Further, the fact that Periasamy et al. demonstrated the embryonic lethality of a homozygous Serca2 knockout in mice does not teach away from making the mouse as claimed. While Periasamy et al. found that lack of SERCA2 function during embryonic development is lethal, the motivation provided by Periasamy et al. to investigate the loss of function of the SERCA2 gene in adult heart would have led the skilled artisan to combine the teachings of Periasamy et al. with those of Sohal et al., whose inducible and cardiac tissue specific tamoxifen Cre-Lox system can be used generate disruptions in genes known to embryonic lethal, such that the effects of the loss of SERCA2 on cardiac function in the adult could be observed. Thus, Sohal et al. provides a specific system to overcome the problems with embryonic lethality experienced by Periasamy et al. such that it would have been

obvious to the skilled artisan at the time of filing to use the inducible and cardiac tissue specific tamoxifen Cre-Lox system to produce an adult homozygous Serca2 knockout to study the effects of loss of Serca2 on cardiac function. Further, based on the testimony of Dr. Wuytack et al., it would appear that the skilled artisan would have expected that homozygous knockout of the Serca2 gene in an adult heart would not result in instant lethality, but rather there would have been a reasonable expectation that the mice would survive for about one week.

Finally, it is reiterated that the any evidence of "unexpected results" must be commensurate in scope with the claimed invention. MPEP 716.02. The specification discloses a single transgenic mouse in which both endogenous genomic copies of the SERCA2 gene contain two loxP sites flanking exons 2 and 3, and whose genome further comprises a MerCreMer transgene under transcriptional control of the α-MHC promoter, wherein the administration of tamoxifen result in the Cre mediated deletion of exons 2 and 3 in both copies of the SERCA2 gene, and wherein the mouse develops heart failure by day 52 following tamoxifen administration. There is no evidence of record for any other embodiment of the claimed invention which demonstrates the alleged "unexpected" survival for more than 50 days. The claims as written are not limited to a transgenic mouse in which both endogenous genomic copies of the SERCA2 gene contain two loxP sites flanking exons 2 and 3, and whose genome further comprises a MerCreMer transgene under transcriptional control of the α-MHC promoter, wherein the administration of tamoxifen results in the Cre mediated deletion of exons 2 and 3 in both copies of the SERCA2 gene, and wherein the mouse develops heart failure by day 52 following tamoxifen administration. The claims as written are broad, as discussed in detail in the above paragraphs, and further do not include any limitation regarding the length of survival of

the homozygous Serca2 knockout mouse. As such, applicant's arguments are not found persuasive in overcoming the rejection for reasons of record.

No claims are allowed.

Any inquiry concerning this communication from the examiner should be directed to Anne Marie S. Wehbé, Ph.D., whose telephone number is (571) 272-0737. If the examiner is not available, the examiner's supervisor, Joseph Woitach, can be reached at (571) 272-0739. For all official communications, the technology center fax number is (571) 273-8300. Please note that all official communications and responses sent by fax must be directed to the technology center fax number. For informal, non-official communications only, the examiner's direct fax number is (571) 273-0737. For any inquiry of a general nature, please call (571) 272-0547.

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Dr. A.M.S. Wehbé

/Anne Marie S. Wehbé/
Primary Examiner, A.U. 1633